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EXAMINER	
KELLY, ROBERT M	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,409	KIEFFER ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *89-113* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 31,34-36,38,40,43,47-49,51,52,54,55,71-73,76,78-80,82,83 and 85-113.

DETAILED ACTION

Applicant's amendments and argument of 10/11/05 have been entered.

Claims 1-30, 32-33, 39, 44, 50, 53, 74-75, 77, 81, and 84 are cancelled.

Claims 31, 34, 36, 38, 43, 47, 51-52, 54, 71-73, 76, 78, 82-83, and 85 are amended.

Claims 87-113 are newly added.

Claims 31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-113 are presently pending.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Election/Restrictions

New Claims 87-88 are drawn to the elected invention.

Newly submitted claims 89-113 are directed to an invention that is independent or distinct from the invention elected, without traverse, in the election of 9/18/02. Specifically, the restriction requirement of 8/13/02 required restriction of *ex vivo* methods (Group II), from that of direct administration of a polynucleotide (Group III). Applicant clearly elected Group III (election of 9/18/02), without any traversal (Official Action of 12/18/05, p. 2).

Accordingly, claims 89-113 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Therefore, claims 31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-88 are presently considered.

This application contains claims 89-113 drawn to an invention nonelected without traverse, as reviewed above. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Status, Cancelled Claims

In light of Applicant's cancellation of claims 1-30, 32-33, 39, 44, 50, 53, 74-75, 77, 81, and 84, all pending rejections and/or objections to these claims are rendered moot, and thus are withdrawn.

Claim Objections

Claims 47 and 78 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is clear that the transformed cells of the parent claim are necessarily present in a tissue or organ of the gastrointestinal tract, and as such, the dependent claim to such subject matter is necessarily not further limiting.

Claim 52 and 83 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. All endocrine cells are necessarily progeny of stem

cells, pluripotent progenitor cells, and/or multipotent cells, and as such, the claim does not further limit the parent claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31 and 71 each recite the limitation "gut or gastrointestinal mucosal tissue endocrine [cell or cells]". Such limitation appears to encompass any cells of the gut, or any gastrointestinal endocrine cells, which are in the subject. However, it is clear from Applicant's argument that Applicant is actually attempting to claim "gut mucosal tissue endocrine [cell or cells] or gastrointestinal mucosal tissue endocrine [cell or cells]" (e.g., Argument of 10/11/05, e.g., p. 20, paragraph 4). Hence, this limitation appears to lack clarity in what Applicant is claiming.

Claims 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 72-73, 76, 78-80, 82-83, and 85-88 are rejected for depending from rejected base claims and not overcoming the lack of clarity in such base claims.

Claim Rejections – 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-86 remain rejected, and Claims 87-88 are newly rejected, under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for reasons of record, e.g., in the Official Action of 4/7/05. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 43 and 76 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The new basis of rejection is based on the claiming of variants and subsequences of the chromogranin A promoter, necessitated by the amendment.

In order to help Applicant understand the prior rejection, the prior rejection is readdressed, using a newly-directed formula provided by the PTO. This is followed by the rejection on the new grounds of the Chromogranin A promoter.

Rejections based on a generic "sugar, polypeptide, amino acid or fat"

Applicant's claims encompass any sugar, polypeptide, amino acid, or fat that induces the production of a protein operably linked to either a GIP promoter, a chromogranin A promoter, or any fragment or variant thereof that has all or any part of any expression function of the full-

length native GIP or chromogranin A promoter. (E.g., Claims 1 and 71, and further claims 43 and 76.)

Applicant's specification provides that any "nutrient", for example, sugars (e.g., glucose, lactose, sucrose, fructose, mannose, etc.), carbohydrates, starches, fats, lipids, fatty acids, triglycerides, polypeptides, amino acids, cellulose, hormones, vitamins, and minerals, may modulate translation, transcription, or stability of the protein (SPECIFICATION, p. 16, paragraphs 1-2), and that splicing, message stability, etc. (SPECIFICATION, p. 18, paragraph 5) may also be effected. Moreover, the term production, which is also used in the claims, refers to any effect on expression or secretion of the protein encoded (SPECIFICATION, p. 19, paragraph 2). Hence, these nutrients may increase expression or secretion of the protein, by any method which influences translation, transcription, stability, splicing, message stability, secretion, and anything else involved in getting the protein from the point of beginning transcription to the point of action of the protein on its intended target(s). Hence, Applicant's claims encompass anything that produces the desired effect, even an amino acid used in the making of the insulin or leptin which is manufactured, sugars used to make energy which is then used to make the transcript, translation product, in post-translation modification, or even secretion of the protein.

However, in further examination of the specification, it is clear that the bulk of the information is provided for the GIP promoter, and its induction by glucose (e.g., EXAMPLES). Hence, while providing a broad description for anything that produces the desired effect, Applicant has only provided such structure of the GIP promoter (e.g., p. 13, paragraph 2), which is required for induction by glucose (Id.).

Applicant's specification only describes an actual reduction of a two embodiments: the increase of transcription of a protein linked to the GATA-containing GIP promoter (e.g., p. 13, paragraph 2 and EXAMPLES), and a vitamin D response element which increases transcription of operably linked sequences in the presence of vitamin D (pp. 17-18, paragraph bridging). However, such vitamin D response element is irrelevant to Applicant's claims, as Applicant does not claim the vitamin D response element. Moreover, with these two examples, it appears to the Artisan that Applicant is not in possession of the broad generas claimed, but only the idea of a nutrient that induces transcription from a promoter, as that is what these promoters do, induce transcription.

Applicant's invention is not shown to be complete by a reduction to drawings or structural or chemical formulae of sufficient detail to show possession of the claimed invention as a whole, because such single relevant embodiment does not demonstrate such the possession of any sugar, polypeptide, amino acid, or fat that induces any of the properties required to fit the term "production" of the operably linked polypeptide linked to the GIP or chromogranin A promoter. Applicant has only demonstrated possession of glucose induction of the GIP promoter. Hence, a sufficient number of embodiments have not been disclosed such that the Artisan could determine that Applicant possessed the genera.

Considering that Applicant has only disclosed a single embodiment relevant to the claims, that of glucose inducing the GIP promoter to increase transcription, Applicant's claim to any such sugar, polypeptide, amino acid, or fat that induces any of the myriad of properties listed in the specification, the Artisan could not, even having a high level of skill in the art, determine that Applicant possessed the various genera claimed for the promoters and proteins claimed.

Rejections based on a generic "subsequence or variant of the chromogranin A promoter"

Applicant's claims encompass any subsequence or variant of the chromogranin A promoter.

The specification makes a single mention of the chromogranin A promoter, in TABLE 1, page 15, as an exemplary promoter and/or enhancer for targeting expression of proteins to endocrine cells in the gut, along with eleven other promoters and/or enhancers. With regard to subsequences and variants, while the specification does provide some description of the requirements for a subsequence or variant of the GIP promoter, which has at least some activity of the wild-type promoter (i.e., being responsive to glucose) (p. 13, paragraph 2), absolutely no description is provided for the minimal requirements of a chromogranin A promoter are provided, nor is there even any description as to what nutrient(s) increase and/or decrease expression from any chromogranin A promoter so that the Artisan might determine which parts of the chromogranin A promoter are required for its induction/repression, much less the variants and subsequences claimed. Hence, although the specification discusses broadly the use of any gut endocrine promoter (e.g., pp. 9-10, paragraph bridging), and by way of example, the GIP promoter (whole specification), the only description of the chromogranin A promoter is a single mention of it in Table 1, along with eleven other promoters. Therefore, the further extrapolation of the chromogranin A promoter subsequences and variants, without any further description appears to not be possessed after reading the specification.

With regard to a reduction to practice, Applicant has not demonstrated a single production to practice, even by way of transgenic animal, for the chromogranin A promoter. Moreover, Applicant's constructive reduction to practice is similarly incomplete, being limited to

the single mention of chromogranin A in Table 1. Hence, Applicant has not provided the complete description of the invention of any single subsequence and/or variant, or any relevant identifying characteristics.

Therefore, due to the lack of any particular subsequence and/or variant, and given the level of variability claimed, without any physical or chemical properties, except that the promoter has some part of the activity of a wild-type chromogranin A promoter, and further such activity is not coupled with any known or disclosed structure except that of the full-length chromogranin A promoter, the Artisan could not determine that Applicant had possession of any subsequence or variant of the chromogranin A promoter.

Response to Arguments – Written Description

Applicant's arguments of 10/11/05 have been fully considered, but are not found persuasive. (It should be noted that the subsequences and variants of the chromogranin A promoter are a new basis of rejection, and as such, Applicant's arguments do not address such basis of rejection, but only the various nutrients claimed.)

Applicant argues that the specification only needs to appraise the Artisan of the invention in sufficient detail to demonstrate that Applicant had possession of the invention, but does not require a disclosure of every species encompassed, even in an unpredictable art. Therefore, Applicant argues, a description of every sugar, polypeptide, amino acid and fat that induces production of the protein is not required. (Applicant's argument of 10/11/05, p. 9, last paragraph-p. 10, paragraph 2.)

Such is not persuasive. While the Examiner agrees with Applicant's argument, the Examiner argues that the breadth of what is a sugar, polypeptide, amino acid, or fat that is

encompassed by the claims is so broad as to encompass anything with the desired effect, even to the point of providing building blocks for production of the protein, or energy for making/secreting the protein. Moreover, Applicant's specification only describes induction of two promoters, by a single molecule in each case. As such, even though the structure of a sugar, polypeptide, amino acid or fat is generally known in the art, the specific structure required to induce production of the insulin or leptin is not determined by the Artisan to be possessed by Applicant. Applicant is not required to provide all species of the genera, but a sufficient number of species of the various genera that work to increase production of the protein, and thereby treat the subject, such that the Artisan could determine possession of the genera.

Applicant argues that the disclosure of specific embodiments, i.e., glucose acting to increase transcription from the GIP promoter, and vitamin D acting to increase transcription from the vitamin D response element, that the skilled artisan would know the generic structures as well as specific examples of nutrients that induce production of the protein (pp. 10-11, paragraph bridging).

Such is not persuasive. While Applicant has provided two specific examples, each of these is directed to transcription induction, as this is what the GIP promoter and vitamin D response element provide, they do not provide anything to do with secretion, translation, splicing, energy, or the other myriad of things which is encompassed by the claimed sugars, polypeptides, amino acids, or fats requirement to increase production of the protein. Moreover, such does not even demonstrate a single nutrient that induces production from the chromogranin A promoter through transcription, much less the other myriad of mechanisms discussed.

Applicant argues that the breadth of nutrients claimed that induce production of a protein, by virtue of either increased gut endocrine promoter expression or increased gut endocrine promoter secretion, is possessed, as demonstrated by a list of 25 articles directed to various sugars, carbohydrates, fats, amino acids, and polypeptide derivatives (Applicant's argument of 10/11/05, p. 11, paragraph 3).

Such is not persuasive. Applicant has not provided the listed articles, nor demonstrated how they provide sufficient relevant identifying characteristics for the generas of any sugar, polypeptide, amino acid or fact that increases production of the protein which is produced by the GIP or chromogranin A promoter. Therefore, Applicant's argument is not considered.

Applicant rehashes the argument that a sufficient number of species have been disclosed, that the specification and art describe a relevant number of species of each genera, and the Aritsan would therefore know that Applicant possessed the invention (Applicant's argument of 10/11/05, p. 12, paragraphs 2-3).

Such is not persuasive. Applicant has disclosed only a few promoters activated by a single molecule in each case, and disclosed that production of the protein, in broad terms, can be increased at any point by any of the molecules, either directly or indirectly, and thereby claims the broad generas to increase production of the protein. However, upon reviewing Applicant's broad disclosure, it is clear to the Artisan that Applicant possessed the GIP promoter and glucose for induction of transcription from such promoter, and that the other various mechanisms of influencing the production of the protein are simply an envisioning of ideas, not an actual possession of the claimed invention.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 34-36, 38-40, 43, 47-49, 51-55 and 87 remain and/or are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method of ameliorating the symptoms of diabetes in a mammal having diabetes due to a loss of pancreatic beta, insulin-secreting, cells, comprising contacting duodenal mucosal tissue K cells in the mammal with an FIV vector comprising a transgene encoding human insulin, operably linked to the GIP promoter, which cells were transformed by intra-luminal incubation of the duodenum, with a sugar that induces production of the insulin by the transformed cells, such contacting by administration of glucose, orally, thereby causing release of insulin into the blood and amelioration of the diabetes, does not reasonably provide enablement for any treatment of diabetes or its onset, any animal, any chromogranin A promoter, any mucosal endocrine cell, any polypeptide, any animo acid, or any fat, any production of insulin, or any method of transforming the subject via intra-cavity delivery with any vector, any vector, any method of nutrient contacting, or any mucosal endocrine cell of the GI tract or gut, for reasons of record in the prior Official Actions as well as the new grounds provided below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 71-73, 76, 78-80, 82-83, 85-86, and 88 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record

and/or for reasons necessitated by the amendments. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Below, the enablement rejections are readdressed, with due regard to the new bases of the rejections, followed by an answer to Applicant's arguments. Further, in order to help Applicant understand the rejection, more references have been applied, but many of the same bases of rejection remain, and those new bases of rejection were necessitated by Applicant's amendments.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope. (It is noted that this is written as a scope of enablement, but that scope provided demonstrates a complete lack of enablement for obesity/undesired body mass.)

The Breadth of the Claims

Applicant's claims are broad in many aspects which the Artisan would not find enabled for their broad scope. Below is an analysis of the breadth of the claims.

Claims 31, 34-38, 40, 43, 47-49, 51-52, 54-55, and 87 encompass any treatment of any subject having, or at any risk of having, diabetes, comprising contacting any gut or gastrointestinal mucosal tissue endocrine cell in the subject, which cell has been transformed to comprise a GIP or chromogranin A promoter in operable linkage with a sequence encoding insulin by any form of intra-cavity delivery of the construct, with any sugar, polypeptide, amino acid, or fat that induces production, by any mechanism, of the insulin by the cells, which causes any decrease in the amount of blood glucose in the subject. Dependent claims 34-36 limit the type of diabetes to type 1 or type 2 and subjects having fasting plasma glucose greater than 110 mg/dL (which is a level of a diabetic, not a subject at risk of having diabetes). Claim 38 limits the sugar, polypeptide, amino acid, or fat to increasing the expression (e.g., transcription, translation, splicing, and delivery), or the secretion of the insulin. Claim 40 requires the secretion of insulin to be increased in the endocrine cells. Claim 43 limits the promoters to being any portion or variant of the promoters in the base claims that has any part of the wild-type promoter's expression function (which is any form of translation). Claim 47 limits the endocrine

cell to being present in a GI tract tissue. Claims 48-49 limit the tissue to intestinal or gut. Claim 51 limits the endocrine cells to K, L, S, G, D, I, Mo, GR, or entero-endocrine cells, which are all endocrine cells of the GI tract. Claim 52 requires the cell to be the progeny of any stem cell, any pluripotent progenitor, or any multipotent progenitor cell, which all somatic cells are. Claim 54 requires the transforming construct to be any vector. Claim 55 requires the vector to be any viral vector.

Claims 71-73, 76, 78-80, 82-83, 85-86, and 88 encompass any treatment of any subject having, or at risk of having, any undesireable body mass, or obesity, comprising similar transformations as claim 31 with a polynucleotide of the same promoters, operably linked to a sequence encoding leptin, then contacting the cells with any sugar, polypeptide, amino acid, or fat that induces the production of leptin by the cells in any amount effective to treat the body mass or obesity. The dependent claims roughly track the same language as the dependent claims to claim 31.

However, because these claims are broad for treating any subject, any level of treatment, any prophylactic treatment, the use of any sugar, polypeptide, amino acid, or fat (hereinafter referred to as "nutrient"), which nutrient increases any production of the protein, any vector type, any intra-cavity administration of the vector, any method of administering the nutrient, any mucosal endocrine cell of the GI tract or gut, any chromogranin A promoter, in any animal, and for treating any obesity, the Art itself would be required to disclose quite a large amount of information in order to allow the Artisan to practice the invention without having to perform undue experimentation to find the working embodiments encompassed, and therefore essentially inventing Applicant's claimed invention for Applicant. However, the Art and Applicant's

specification and Examples do not provide such information, and hence, the Artisan would have to perform undue experimentation to practice the working embodiments. Such analysis is shown below.

The Nature of the Invention and State of the Prior Art

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an

immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Also, Anderson (1998) Nature, 392 (Supp.), pp. 25-30, similarly states "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease (p. 25, col. 1) and concludes "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after the genes are delivered" (p. 30). Besides the general expectation that it will require years of further research to

develop effective gene therapy (p. 30), it would require extensive research to understand the fundamental biology of the system.

Moreover, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art (e.g., Official Action of 12/18/02, pp. 8-9).

Further the vectors must efficiently target and transform enough of the tissue which is to be targeted, as noted above, however, it is clear that any particular vector may have a lower ability to transform any particular cell type, and further, even within vector types, the tropism of any particular vector may be distinct, disallowing enough transformation to take place. Such is disclosed in Ma, et al. (2001) Curr. Pharma. Biotechnol., 2: 1-17, disclosing that the various non viral vectors are less efficient than viral vectors (e.g., ABSTRACT), and the various forms of non-viral vector have different efficiencies of gene transfer (body of document). Moreover, by way of example, van Beusechem, et al. (2000) Gene Therapy, 7: 1940-46 discloses that even within the strains of a single virus type, tropisms may be greatly varied (e.g., ABSTRACT). Hence, the use of any particular vector would not necessarily demonstrate that another type of vector would be efficacious as any other vector would have its own targeting and transformation ability.

Further, with regard to administration route of any molecule, similar problems with targeting the tissue apply. Langer, et al. (2003) Scientific American, 288(4) : 50-57 reviews the application of drugs to patients. Langer finds many of the same difficulties, e.g., with route of administration (e.g., p. 52, col. 3, paragraph 2), barriers to targeting (e.g., p. 52, col. 2, paragraph 1), clearance (e.g., p. 52, col. 1, paragraph 1), as well as many other problems (article in general),

which essentially amount to the same arguments made above with respect to gene therapy: it simply isn't reasonably predictable that by any particular route of administration that enough cells will be effected for a long enough period of time to effect treatment.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, encoding specific GDNF proteins, under the control of specific promoters and other control elements, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements. Further, from this we see that the problems with targeting are compounded and hence even less reasonably predictable when administering a second compound to contact the same cells that were transformed. Both the vectors and the nutrients must reach the exact same cells, and hence, it is even less reasonably predictable that through distinct routes of administration, the nutrient will reach the same cells that were transformed.

With regard to treatment and prevention of diabetes, the state of the Art of diabetes gene therapy suggests that while some progress has been made to date there are issues that remain, which make the treatment of diabetes by gene therapy unpredictable. Yoon, et al. (2002) Trends in Mol. Med., 8(2): 62-68 discuss the recent progress made in the field of IDDM. Yoon suggests

that a possible treatment is the development of beta-cell substitutes by introducing an insulin-producing gene into non-beta cells, which would evade the beta-cell specific autoimmune attack. However, use of non-beta cells for insulin production has not been feasible due to lack of an appropriate glucose-sensing system to regulate insulin transcription, enzymes that process the insulin, and glucose-regulatable exocytosis in the target cells (ABSTRACT). According to Yoon, an effective insulin gene transfer system is necessary for successful insulin gene therapy. Yoon goes on to discuss various viral and non-viral systems for gene transfer of insulin (repeating some of the issues addressed above, making them directly apply to insulin) (pp. 62-64). The major hurdle for effective insulin therapy, Yoon states, is the lack of highly regulated biosynthesis and secretion of transgenic insulin in non-beta cells (pp. 64-65). Another important problem that must be overcome for insulin gene therapy to be effective is the ability of a non-beta cell to produce biologically active insulin. As discussed by Yoon, preproinsulin must undergo several stages of processing before biologically active insulin is produced; the problem being that most non-beta cells lack the beta-cell specific endoproteases that convert proinsulin to insulin (pp. 65-66). Finally, Yoon stresses the need to identify and utilize a target cell, having the same characteristics specific to the production of insulin (pp. 66-67). It appears that the K cell has emerged as a target cell that may potentially be the missing piece in the puzzle for effective insulin gene therapy because of its ability to process proinsulin to insulin. Yoon comments on the instant inventor's work, which demonstrated that mouse K cells can produce human insulin (p. 66, col. 2, paragraph 3). Yoon concludes that an effective means of gene delivery to K cells needs to be developed for *in vivo* gene therapy to be successful for diabetes treatment.

Hence, from Yoon, we see that Applicant's K cell appears to be the only player potentially able to produce insulin which the Artisan would find potentially able to be of use in treating diabetes. The other types of cells, e.g., the Mo cell, would not be predicted to produce such proper processing. Moreover, Yoon recognizes the need for highly-regulated biosynthesis and secretion of the insulin to effect treatment, and as such, Applicant's simple disclosure of glucose affecting the transcription of the insulin gene in such cells when driven by the GIP promoter only provides for increases in transcription, not the commensurate other aspects of production which Applicant envisions. In essence, it would be undue experimentation to find the working embodiments of the various genera of nutrients now claimed to find those that work with the GIP promoter and/or chromogranin A promoter (of which none are disclosed).

Corbett, et al. (2001) Trends Endocrinol. Metabol., 12(4): 140-42, support the conclusions of Yoon in commenting on the instant inventors work. Corbett reports that transgenic mouse K cells can produce human insulin and in doing so have the ability to normalize glucose homeostasis in diabetes and in response to a glucose challenge. Corbett suggests that K cells might be an excellent cellular target for gene therapy but at the same time reiterate Yoon, stating that methods for gene delivery to gut, where the K cells are normally found, have not yet been developed. Corbett further discusses that for gene delivery to the gut to be successful, K-cell progenitor or stem cells need to be the target of gene therapy because of the rapid rate at which the gut epithelial lining is shed (p. 141). In the long term, Corbett posits that gene therapy approaches targeting glucose responsive K cells could provide a novel and attractive method for the treatment of patients with diabetes. Corbett raises a final issue regarding insulin gene therapy, which is the fact that insulin is an autoantigen identified in

patients with new onset of IDDM and in the NOD mouse model of autoimmune diabetes, from which insulin-reactive T cells have been isolated. In light of such, Corbett cautions that K cells engineered to produce insulin could also become the targets of autoimmune mediated destruction, an event that could also result in gut inflammation. The inventor's own publication (Cheung et al) while reporting the results outlined above by Yoon and Corbett suggests that genetic engineering of K cells to secrete insulin may represent a viable mode of therapy for diabetes in the future (p. 1961).

In light of the above, it appears that the prior art and nature of the invention suggest that insulin gene therapy might be feasible in the future. However, many difficulties are yet to be surmounted, including vector types, vector targeting, transformation of enough cells, production of enough mRNA and protein therefrom, under a properly regulated expression and secretion, for a long enough period of time, without immune responses destroying the transformed cells, for therapy to take place.

With regard to treating obesity/unwanted body mass, in addition to the same problems above with regard to gene therapy (such is necessarily true, as it still has the same hurdles to overcome), the art generally recognizes that the results with treatment with leptin are specious at best, and not reasonably predicted by the Artisan to be efficacious for any obesity/unwanted body mass. To wit, Buettner, et al. (2000) Am. J. Physiol. Endocrinol. Metab., 278: E563-69 report "the ability of leptin administration to reverse metabolic abnormalities in the ob/ob mouse and improve insulin action in normal animals has lead to the proposal that leptin may serve as an effective therapy for human obesity." Buettner goes on to caution that before leptin can effectively be used to treat obesity a number of questions remain to be answered. "First, it is not

clear that increasing plasma leptin levels will be sufficient to correct the metabolic abnormalities associated with obesity, principally insulin resistance and perturbed lipid and carbohydrate metabolism. Second leptin therapy involving multiple injections has had mixed results both in animal models of obesity and in human trials, and this suggests that alternative strategies such as sustained increases in plasma leptid should be considered." (p. E556). Moreover, Chiesi, et al. (2005) Trends in Pharmacol. Sci., 22(5): 247-54 provides a recent review of the field, demonstrating that such therapies with leptin are similarly not even now considered to be reasonably predictable. To wit, Chiesi discusses the discovery of leptin, its nature as a feedback regulator, and mouse models which seemed to indicate that it would treat obesity, followed by a small trial where a patient was treated (p. 247, paragraph bridging columns). However, subsequent clinical trial indicated leptin was much less promising than expected (Id., col. 2, paragraph 2), where, even after extremely high doses, weight loss was variable, and average reductions in weight were small (Id.). The author explains many reasons why such results may be found, including, for example, leptin's activity may be at very low concentrations, and increases have no effect, therapeutic efficacy may have been overestimated, human responses are not the same as the mouse, some humans may be resistant to leptin, either due to leptin receptor signaling or transportation of leptin in the body (p. 247, col. 2, paragraph 3). Moreover, Liu, et al. (2005) Drugs of Today, 41(5) : 345-62 adds another complication: obesity and unwanted body mass are actually unlike other genetic diseases, being under the control of many genetic factors (p. 351, col. 2, paragraph 2). Hence, from this, the Artisan could not reasonably predict that any particular obesity or unwanted body mass could be treated, much less detected before

obesity occurs such that treatment could be effected, because it is simply not understood well enough, and further a single gene may not be enough.

With regard to the use of the chromogranin A promoter in such K cells, the chromogranin A promoter is not normally expressed in such K cells, but in ECL cells, which are not predicted to be able to process the insulin (ABOVE), and further, as such, the pathways to activate chromogranin A by a the known nutrient, NGF, are not reasonably predicted to be present (Hocker, et al. (2000) Gastroenterol., 121(1): 43-55 and Mahata, et al. (1999) Neuroscience, 88(2): 405-24, p. 405), and this is confused by the fact that the Artisan does not even know with reasonable predictability that pathways required for its activation in any particular cell type. Further, the proximal activator of chromogranin A promoter appears to be cAMP, but several polypeptides, and of course, indirectly, amino acids to make them, and sugars and fats to make the polypeptides and provide energy to make them, are involved. To wit, nerve growth factor is involved Mahata, et al. (1999) Neuroscience, 88(2): 405-24, p. 405, and such factor is likely to digested if administered orally, before it reaches it site of action (ABOVE). Moreover, the proximal factor that produces more transcription from this promoter is actually cAMP, which is not a nutrient in any class claimed (Id.). Also, it appears that from Mahata, the pathways for such activation by NGF are restricted to the neurons (p. 406). Hence, the activation for L-cell transcription by chromogranin A may be very distinct, and appears to be unknown. Even if the cells had the proper machinery to effect transduction and reponse to such NGF, the administration of such NGF protein is still not reasonably predicted to turn on chromogranin A, except in the case of direct contact, as it has already been established that protein administrations face several barriers, as further reviewed by Langer (2003) Sci. Am., 4: 52-57, which preclude

the targeting of the proper cells. Such can further be extrapolated to any administration of any particular substance also. Lastly, even if such nutrients could be found that activate chromogranin A, and further reach the target cells through predictable routes, it is still not reasonably predictable that such activation would be sufficient for therapy. Therefore, outside of the demonstration of glucose reaching the GIP-insulin-containing target cells in the duodenum, as shown in the specification and declarations, via oral administration and direct administration, no other form of administration, and no other form of nutrient would be reasonably predicted to reach the transformed target cells in large enough amounts and for a long enough time to have a therapeutic effect (similar to the gene therapy arguments above).

The Guidance and Direction Provided by Applicant

The background of Applicant's specification broadly discusses the difficulties in the use of protein treatment of disorders in general (pp. 1-2) (which expounds the same difficulties with delivery as that found for the use of any nutrient in general), the use of gene therapy, and the difficulties surrounded by these methods (pp. 2-3), the need for regulated gene expression in certain gene therapy protocols, including diabetes (p. 3), a review of diabetes and the proposal to use surrogate cells for the production of insulin in diabetes treatment by gene therapy, and further emphasizing the need to control production of insulin in diabetes and in other diseases in humans, which is proposed to be satisfied by the invention (pp. 3-4).

The summary of the invention claims that the invention is based, in part, on the production of transformed gut cells that produce insulin, which are able to secrete insulin at physiological levels and restore normal glucose homeostasis in diabetic animals. From this, Applicant summarizes that cells may be transformed with any transgene which will work in

similar manner to be controlled to provide a benefit in any disorder. Further, the mucosal cells respond to any nutrient, and may be anything causes increased expression and/or secretion of the transgene.

The specification broadly discusses expression of transgenes in endocrine cells releases the encoded protein into the bloodstream in a regulated manner (pp. 10-11), delivery of GIP linked to human insulin in transgenic mice demonstrates expression and secretion of insulin in the K cells of such mice (p. 11), methods of generating a mucosal cell producing such protein in a regulated manner by a nutrient, which mucosal cell may be any endocrine or non-endocrine cell or any non-fully-differentiated cell (p. 11), vectors (p. 11), various expression control elements (p. 12), GIP promoters which respond to glucose (p. 13), examples of 12 other promoters and/or enhancers for targeting expression to endocrine cells in the gut, including the only mention of chromogranin A (TABLE 1), discussion of various other expression elements, and response to nutrient to decrease or increase expression of operably linked sequences (p. 15), discussion of nutrients, which may be anything and have any effect to affect production of the protein (p. 16), functional fragments and variants of promoters (p. 16-17), broad mention of many genes that may have promoters that are regulated by other nutrients (p. 17), bacterial nutrient regulated elements (p. 18), non-nutrient response elements (p. 18), a definition of operable linkage (p. 18), a definition that expression control can be effected at transcription, translation, splicing, message stability, etc. (p. 18), a definition that production encompasses expression or secretion, and that such may similarly be effected by the same as the expression control definition (p. 19), additionally signals or stimuli may similarly increase production, and the even if the promoter is not regulated, secretion may be regulated by the stimuli (p. 19),

various definitions (pp. 20-21), various transgenes (pp. 21-22), obesity and leptins (p. 23), more transgenes (pp. 23-24), various cell types which are encompassed (pp. 24-26), various definitions, the use of any cell which is adapted grow in mucosa or other tissue, the use of multiple transgenes, transgenic animals, treatment of various disorders, more definitions, methods of introduction of the transgene, pharmaceutical formulations, administrations, stem cells, and instruments for administration (pp. 26-42).

However, such broad discussion does not provide the specific guidance and direction for the Artisan to reasonably predict whether any particular vector, administered to any particular cavity in any animal with the appropriate transgene would target enough of a cell that could properly process the insulin, produce enough stable and functional mRNA therefrom, and protein therefrom, and be secreted in large enough amounts for a long enough period of time to effect treatment. Moreover, it is apparent from reading the prior art, and Applicant's specification, that the claim to exposing the sugar, protein, amino acid, or fat to the cell is in order to produce the required regulated production to effect proper treatment. However, while Applicant has provided a single sugar, glucose, which affects the GIP promoter, Applicant has not demonstrated a single chromogranin A promoter effector, anywhere, that produces any particular production of proteins driven therefrom, nor has applicant disclosed any other specific form of increasing production. Hence, the use of the Chromogranin A promoter, without demonstration of any particular pathway and effector for that pathway to increase its production, and without any demonstration of a polypeptide or fat or sugar that increases any of the other aspects encompassed by the claims, that the Artisan would face a myriad of possible nutrients in each of the genera, of which the vast majority would be predicted not to produce the proper response in

production. Hence, if anything, the disclosure adds to the lack of reasonable predictability, and such similarly applies to the various nutrients and the GIP promoter, where only glucose is shown, and the Art demonstrates such unpredictability.

Existence of Examples

Applicant's specification provides three real examples, and a single prophetic example. Example 1 demonstrates the isolation of K cells from a mixed population of tumor tissue derived from a mouse, by expression of GFP from the GIP promoter, which cells, when transformed with another construct of GIP promoter linked to insulin produced insulin in a glucose-dependent manner *in vitro*. In contrast, other cells similarly transformed with the GIP-insulin construct did not produce significant insulin mRNA.

Example 2 demonstrates that transgenic mice having the GIP-insulin construct in transgenic form express glucose in the duodenum and stomach, in K cells. Example 3 demonstrates these mice to survive STZ-induced diabetes.

Example 4 is a prophetic example of intention to perform *ex vivo* therapy with such K cells.

Three more examples have been provided in the form of declarations of Drs. Kieffer and Cheung, both inventors of the present Application.

The Kieffer declaration demonstrates that GAL-4 promoter linked to leptin, used to transform K cells and placed in alginate, which is then put in a mouse intraperitoneal space, then subcutaneously administered RU486 caused apparent increase in leptin production, and reduced mouse weight, even after removal of the RU486. However, such cells were not transformed *in vivo*, are protected from body by the alginate, are not responsive to a nutrient presently claimed,

and were not transformed by intra-cavity transformation, and further were exposed to an artificial nutrient via subcutaneous implant, and is therefore not responsive to food as would be required by insulin. Further, with regard to leptons, and obesity, the problems art remain that it is not reasonably predictable except for the ob/ob mouse to have treatment in any particular patient of any species.

The Cheung declaration of 6/16/04 demonstrates injection of FIV vectors carrying either chromograninA promoter linked to insulin, or CMV promoter linked to DsRed, and AAV vectors comprising a CMV promoter driving the expression of GFP. The vectors were administered by intraluminal incubation of the duodenum or direct injection into the walls of the duodenum. In the case of insulin production, it was responsive to glucose for 14 days, and the duodenum stained for insulin at day 128. However, these vectors were pseudotyped by VSV-G, and as such their tropisms were decidedly distinct from other vectors, being effective for the K cells, but such does not reasonably predict the transformation of enough cells via any vector, given the lack of reasonable predictability above. Moreover, these vectors were driven by a constitutive promoter with strong expression characteristics, the CMV promoter, and as such even less cells than in the case of the presently claimed promoters need to be transformed. Moreover, the CMV promoter is not responsive to any nutrient, except through the standard indirect methods that Applicant is claiming, but Applicant has not shown any particular nutrient in this case either.

The Cheung declaration of 2/14/05 demonstrates the production of pseudotyped FIV vectors carrying the transgenes of insulin or SEAP, operably linked to the GIP promoter or chromogranin A promoter, respectively. These vectors were used to deliver the genes to cells of

the duodenum by intra-lumenal incubation, in mice. These animals demonstrated production of SEAP or insulin at levels of approximately 15 pM, in blood plasma. Even after 120 days, although some mice had stopped expressing insulin, the others continued to do so, and were the only mice protected from STZ-induced diabetic death when subsequently challenged. However, Cheung's vectors were similarly pseudotyped and hence are not reasonably predictable for any other vector type, for the same reasons as the previous paragraph. Moreover, while Applicant has demonstrated up to 120 days, that some mice expressed insulin, others did not, and given that diabetes may take much longer than four months to develop, it is unpredictable to the Artisan that any animal could be treated prophylactically. To wit, if at 120 days, some animals do not express it, the Artisan could not predict that any animal would express it after a longer time frame, and further, if only some express it, the Artisan could not reasonably predict which patients would express it so that they could be treated.

Further, while Applicant has demonstrated some responsiveness to glucose, it is clear from all these examples that glucose responsiveness it not equivalent and replacing that of a normal islet of langerhans in level and responsiveness. Such is logical because the beta-cells respond not only to glucose but to many other variables of the endocrine system, and as such a single response to glucose is not reasonably predicted to reflect the normal complicated response. Moreover, such does not demonstrate the transformation of another animal's K-cells at a sufficient amount in that other animal, as different animals are of different sizes, requiring more or less expression, and given that the level of expression depends on the number of cells transformed and the production capacity of each cell transformed, it is not reasonably predicted to treat any animal, much less fully treat any animal. However, such is enough to demonstrate

amelioration in mammals, as the mouse model of STZ treatment is recognized to obliterate the cells. On the other hand, as mentioned above, in autoimmune diabetes, these same cells may actually be targeted for producing insulin, and as such, prophylactic treatment is again curtailed.

Moreover, none of these examples, and the previous direction and guidance, demonstrate any delivery of the vector through any other intra-cavity delivery, e.g., sinuses, the complete treatment of diabetes, the prophylactic treatment of real-world diabetes, any sugar, polypeptide, amino acid, or fat that induces production of a polypeptide driven by the GIP promoter except glucose, any sugar, polypeptide, amino acid, or fat that induces production of a polypeptide driven by the Chromogranin A promoter, any form of introduction of any polypeptide, sugar, amino acid, or fat, which will induce production from the various promoters, except glucose administered orally, any animal except mouse, any mucosal endocrine cell except K cells, and the use of any vector, except FIV and AAV vectors, pseudotyped with VSV-G.

Moreover, while Applicant has demonstrated some treatment in ob/ob mice through administration of GTC-1 cells comprising an RU486-Gal4 linked to leptin gene switch, administered to the mouse intraperitoneally, in an alginate gel, the Artisan would recognize this not to translate into treatment of obesity or unwanted body mass in any animal through the gene therapy protocols presently claimed, given the knowledge in the art.

With regard to cell type, Applicant's demonstration of only the K cells producing the insulin in the context of the transgenic mice, and further use of the GIP promoter to isolate K cells from a mixed population similarly bolster the Artisan's opinion that only K cells could produce insulin, and further argue that GIP could only be effective in K cells to begin with.

Lastly, the results fail to overcome the various unpredictabilities in the field, as discussed above, and as such the Artisan would have to experiment to find, with reasonable predictability, the majority of the working embodiments.

The Amount of Experimentation Required

For the reasons discussed above, the Artisan would have to experiment to find, *inter alia*, the cell types, the promoter and nutrient combinations, the methods of administration of the nutrient, the vector types, the duration of efficacious expression, the amount of efficacy (i.e., whether for any particular disorder/onset, the gene would suffice to express with the nutrient sufficiently to produce any particular level of therapy), and to determine whether, for obesity/unwanted body mass, any particular patient would be treatable at all.

Hence, such experimentation is undue, amounting to inventing Applicant's claimed invention for the Applicant.

Conclusion

Because such undue experimentation is found, Applicant's claims are found, alternatively to have a scope of enablement as given above, or to not be enabled at all.

Response to Arguments – Enablement

Applicant's arguments filed on 10/11/05 have been fully considered but are not found persuasive.

Applicant argues that it is clear that STZ is not a real world cause of diabetes, but is reasonably predictive of treatment (Applicant's argument of 10/11/05, p. 16, paragraph 1).

Such is not persuasive. The Examiner agrees with Applicant but given the breadth of the claimed subject matter, including treatment of any animal, and complete treatment of any

diabetes, the rejection was held before. Applicant should note that a scope of rejection was held before, not a full lack of enablement. The Examiner trusts that the above-reiterated rejection will help Applicant understand the rejection better, as it is directed, *inter alia*, the specific promoter use.

Applicant argues that the treatment of children, even though expressing leptin, are treated by administration of leptin, and therefore, the claims are enabled for treatment of obesity and unwanted body mass, as well as risk of its onset (Applicant's argument of 10/11/05, p. 16, paragraph 2).

Such is not persuasive. As has been made of record before, (prior official Actions), as well as above, the results are conflicting, and hence, the Artisan would not reasonably predict any particular patient of any particular species could be treated except ob/ob mice by *ex vivo* methods, as Applicant has demonstrated in their declarations.

Applicant corroborates their argument that treatment works for obesity, with the submission of Heymsfield, et al. (1999) JAMA, 282: 1568 (Applicant's argument of 10/11/05, p. 16, paragraph 3).

Such is not persuasive. The Examiner, and the previous Examiner have shown in the prior actions, and above, that the results conflict with other results, and the Art recognizes that at this time it not understood well enough to predict treatment of any kind in any particular patient of any particular species. The Examiner is not saying it will not work, but that it would be undue experimentation to find those patients that it would work, i.e., make the invention.

Art Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In light of Applicant's amendment and argument, the rejections of Claims 31, 34, 36, 38, 40, 43, 47-49, and 54-55 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,837,693 to German, et al., filed 3/24/95, patented 11/17/98, are withdrawn.

To wit, German does not teach the promoters presently claimed.

31, 34-36, 38, 40, 43, 47-49, 51-52, 54-55, 71-73, 76, 78-80, 82-83, and 85-88

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of Applicant's amendments and arguments, as well as the scope of enablement, the rejections of Claim 31, 43, and 51 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,837,693 to German, et al., filed 3/24/95, patented 11/17/98 and Boylan, et al. (1997) J. Biol. Chem., 272(28): 17438-43, are withdrawn.

Specifically, it was questionable if any of the GI tract endocrine cells would be able to properly process insulin and produce a therapeutic effect in the art (ABOVE, enablement). Hence, a reasonable expectation of success was lacking.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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